REMARKS

I. Status of the Application

Claims 1-5, 7 and 18-23 are pending in the application.

II. Interview Summary

Applicants conducted a telephonic interview with Examiner Spivak on April 17, 2007. Examiner Spivak reviewed a proposed draft amendment and response to the Office Action mailed January 8, 2007 and discussed the same with the Applicants. Examiner Spivak acknowledged that the proposed amendments to the claims addressed the rejection made under 35 U.S.C. § 112, first paragraph. Examiner Spivak recommended amendment to Claim 7 to more clearly recite either the chemical entity or chemical structure of FPL-66564, MDL-100240, and S-5590. Examiner Spivak further recommended amendment of independent Claim 1. Examiner Spivak proposed taking the case to her supervisor to discuss the allowability of the claims and that she would contact Applicants' attorneys within the next two weeks to discuss the outcome of the discussion.

III. The Claims Are Supported By An Adequate Written Description

The Examiner rejected Claims 22 and 23 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement (Office Action, page 3).

Applicants respectfully disagree.

Nonetheless, without acquiescing to any of the Examiner's arguments or rejections and in order to further the prosecution of the present application, Applicants have amended Claims 7, 22 and 23 solely for the purpose of expediting the patent application process and without waiving the right to prosecute the cancelled (or similar) claims in the future.

Applicants respectfully submit that the amended claims are supported by an adequate written description. Applicants respectfully request that the Examiner withdraw the rejections made under 35 U.S.C. §112.

IV. The Claims are Not Obvious

The Examiner has maintained the rejection of Claims 1-5, 7 and 18-21, and extends the rejection to include Claims 22 and 23, under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rodgers et al. (U.S. Pat. No. 6,821,953, hereinafter "Rodgers") in view of The Merck Index; and rejected Claims 1-5 and 18-21 and extends the rejection to include Claims 7, 22 and 23, under 35 U.S.C. § 103(a) as allegedly being unpatentable over Acton et al. (U.S. Pat. No. 6,632,830, hereinafter "Acton") in view of The Merck Index.

Applicants respectfully disagree.

A) Claims 1-5, 7 and 18-21

Without acquiescing to any of the Examiner's arguments or rejections and in order to further the prosecution of the present application, Applicants have amended independent Claim 1, and canceled Claim 5, solely for the purpose of expediting the patent application process and without waiving the right to prosecute the cancelled (or similar) claims in the future. Support for the amendment can be found throughout the Specification, for example, at page 8, lines 26-31 and page 12, lines 5-16, among other places.

Applicants respectfully submit that amended Claim 1, and claims dependent thereon, are not rendered obvious by the cited references. Specifically, the cited references, individually or in combination, do not teach or disclose a method of treating a subject consisting of providing a subject with inflammatory bowel disease, and a therapeutic composition consisting of an angiotensin converting enzyme inhibitor and a physiologically acceptable carrier and/or vehicle, and; administering the composition to the subject under conditions such that the severity of inflammatory bowel disease is reduced in the subject. Furthermore, as described herein as well as in the accompanying 37 C.F.R. 1.132 Declaration of Dr. Daniel H.Teitelbaum, the cited references, individually or in combination, do not reveal a reasonable expectation of success for carrying out the claimed invention to one or ordinary skill in the art.

Applicants respectfully submit that amendment to independent Claim 1 has rendered the Examiner's allegations with regard to Claims 1-5, 7 and 18-21 moot. Applicants respectfully request that the Examiner withdraw rejection of Claims 1-5, 7 and 18-21.

B) Claims 22 and 23

Applicants respectfully submit that rejection of Claims 22 and 23 is in clear, reversible error because the cited references do not disclose each claim limitation the claimed subject matter and they do not reveal a reasonable expectation of success for carrying out the claimed invention. Specifically, the Examiner has not cited to a reference(s) that teaches, discloses or suggests a method of treating a subject comprising providing a subject with inflammatory bowel disease, and a therapeutic composition comprising an ACE inhibitor, and administering the composition to the subject under conditions such that the severity of inflammatory bowel disease is reduced in the subject, wherein reduction of the severity of inflammatory bowel disease in the subject is detectable by an improved histologic colitis score (Claim 22) or the absence of body weight loss of the subject (Claim 23).

1) Rodgers et al. (U.S. Pat. No. 6,821,953) and The Merck Index

The Examiner alleges that Rodgers teaches the administration of ACE inhibitors along with a peptide fragment in various inflammatory conditions of the bowel, such as ulcerative colitis (Office Action, page 4). The Examiner further alleges that the teachings of the cited references suggest the claimed subject matter to a person of ordinary skill in the art and reveal a reasonable expectation of success.

Applicants believe that the Examiner's allegations are unfounded and legally unsupportable.

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)

Rodgers provides a peptide fragment of 3-8 amino acids for treating or preventing damage to mucosal tissue. Rodgers mentions that a method of treating or preventing damage to mucosal tissue with the 3-8 amino acid peptide fragment may also comprise treating with other compounds wherein the other compounds are selected from the group consisting of anti-inflammatory drugs, angiotensin converting enzyme inhibitors, anti-infectives, growth factors, and antihistamines.

However, Rodgers does not teach or discuss how even one of these "other compounds" could be used for the treatment of inflammatory bowel disease. Thus, Rodgers fails to provide

guidance to one of ordinary skill in the art how to use one of the "other compounds" in the treatment of inflammatory bowel disease.

Moreover, as explained in the Declaration of Daniel A. Teitelbaum made under 37 C.F.R. 1.132 submitted herewith, prior to the discovery of the present invention, not one of these "other compounds" had ever been shown (e.g., by Rodgers, the other cited references or anywhere) to be effective in the treatment of inflammatory bowel disease. Thus, the Examiner's allegations regarding Rodgers are not properly scientifically supported and do not provide a reasonable expectation of success for carrying out the claimed invention.[1]

The Examiner's attempt to overcome the deficiencies of Rodgers by citing to The Merck Index does not fix the problem and does not render obvious the present invention.

The Examiner states that

> "a reduction in the characteristics that define an inflammatory bowel disease, such as histological parameters, the presence of heme positive stools, weight loss and clinical severity of colitis are taught by The Merck Index and the qualitative and quantitative determinations of such characterisitics are conventionally examined when a practitioner skilled in the art of gastroenterology ascertains the progression of an inflammatory bowel disease" (Office Action, page 5).

The Examiner fails to acknowledge that whereas The Merck Index might describe weight loss, histological parameters, heme positive stools and clinical symptoms of colitis as being followed in patients with inflammatory bowel disease, The Merck Index **does not** describe or teach use of an ACE inhibitor for the treatment of inflammatory bowel disease, **nor** that an ACE inhibitor can alter weight loss, histological parameters, onset of heme positive stools, and clinical symptoms of colitis when administered to a subject with inflammatory bowel disease.

Applicants respectfully submit that under the Examiner's line of reasoning, it would be obvious that ACE inhibitors could be used to treat any inflammatory disease. However, this is clearly not the case (See Declaration of Applicant made under 37 C.F.R. 1.132). Specifically, Dr. Teitelbaum states that there are hundreds of reports of ACE-inhibitor usage/administration that have actually resulted in inflammatory processes including angioedema, mucosal and small bowel angioedema, tongue ulcerations, and inflammatory disease of the mouth (See Declaration of Dr. Daniel H. Teitelbaum, page 3, second full paragraph). This leads Dr. Teitelbaum to

[1] The Examiner admits "that Rodgers fails to describe a reduction in the characteristics that define an inflammatory bowel disease, such as histological parameters, the presence of heme positive stools, weight loss and clinical severity of colitis." (Final Office Action mailed July 21, 2006, pages 3-4).

conclude that "the numerous publications in the literature that show that a tissue or human's response to ACE-inhibitors may be distinctly different, and completely unpredictable." (See Declaration of Dr. Daniel H. Teitelbaum, page 3, second full paragraph). Thus, prior to the discovery of the present invention, there was nothing in the literature that documented the ability of ACE-inhibitors to provide the claimed benefits.

Applicants submit, for the sake of argument, that even if the references provide a generalized teaching to try to use ACE inhibitors for the treatment of inflammatory bowel disease (something the cited references fail to do), that this is nothing more than an invitation to experiment and does not render obvious Applicants' invention.

"Obvious to experiment" is not the standard for obviousness.[2] The Federal Circuit has made very clear that one must determine whether "the prior art would have suggested to one of ordinary skill in the art that this process **should** be carried out and **would** have a reasonable likelihood of success, viewed in light of the prior art." *Id.* at 1531 (Emphasis added). There is no reasonable expectation of success because there was no way to predict whether an ACE inhibitor could be used to achieve a reduction in the severity of inflammatory bowel disease in a subject (e.g., as evidenced by an improved histologic score or the absence of body weight loss in a subject (See Declaration of Applicant made under 37 C.F.R. 1.132)). Applicants respectfully submit that the Examiner has improperly applied an "obvious to experiment" standard.

Thus, the Examiner has neither established that the cited references suggest the claimed subject matter nor revealed a reasonable expectation of success to one reasonably skilled in the art.

2) Acton et al. (U.S. Pat. No. 6,632,830) and The Merck Index

The Examiner alleges that Acton teaches the administration of an angiotensin converting enzyme (ACE) inhibitor in the treatment of an inflammatory bowel disease (Office Action, page 5) and that in view of the combined teachings of Acton and The Merck Index, it would have been reasonable to expect a reduction in the severity of an inflammatory bowel disease following the administration of an ACE inhibitor (Final Office Action mailed July 21, 2006 at page 5). Applicants respectfully disagree.

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[2] *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988).

The Examiner's rejection is in clear, reversible error.

Specifically, the cited references do not teach, disclose or suggest the claimed subject matter nor do they provide a reasonable expectation of success for carrying out the claimed invention.

The Examiner fails to cite to language within Acton that would allow the skilled artisan background sufficient to practice the instant invention. This is not surprising as Acton does not provide any particular examples of inflammatory bowel diseases that might benefit from administration of an ACE-2 inhibiting compound or any specific administration protocol for how an ACE-2 inhibitor could be used to treat an inflammatory bowel disease (e.g., ulcerative colitis). Acton further fails to provide any examples (*in vitro* or *in vivo*) demonstrating the use of an ACE-2 inhibitor in the treatment of inflammatory bowel disease. Thus, Acton fails to provide guidance to one of ordinary skill in the art regarding how to use an ACE inhibitor for treating an inflammatory bowel disease.[3]

In an attempt to overcome the deficiencies of Acton, the Examiner cites to The Merck Index. However, as discussed above, whereas The Merck Index might describe weight loss, histological parameters, heme positive stools and clinical symptoms of colitis as being followed in patients with inflammatory bowel disease, The Merck Index **does not** describe or teach use of an ACE inhibitor for the treatment of inflammatory bowel disease, **nor** that an ACE inhibitor can alter weight loss, histological parameters, onset of heme positive stools, and clinical symptoms of colitis when administered to a subject with inflammatory bowel disease.

Thus, the Examiner's rejection is in clear, reversible error because there exists no clear direction or guidance provided by Acton or The Merck Index, individually or combined, rendering obvious to one skilled in the art the ability to use ACE inhibitors for the treatment of inflammatory bowel disease, nor a suggestion that such treatment would provide a beneficial result.

Applicants submit, for the sake of argument, that even if the references provide a generalized teaching to try to use ACE inhibitors for the treatment of inflammatory bowel disease, that this is nothing more than an invitation to experiment and does not render obvious Applicants' invention.

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[3] The Examiner admits "that Acton fails to describe a reduction in the characteristics that define an inflammatory bowel disease, such as histological parameters, the presence of heme positive stools, weight loss and clinical severity of colitis." (Final Office Action mailed July 21, 2006, pages 4-5).

However, as referenced above, "obvious to experiment" is not the standard for obviousness.[4]

There can be no reasonable expectation of success because there was no way to predict whether an ACE inhibitor could be used to achieve a reduction in the severity of inflammatory bowel disease in a subject. Thus, the Examiner has neither established that the cited references suggest the claimed subject matter nor revealed a reasonable expectation of success to one skilled in the art.

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness due to the inability to provide references, alone or in combination, that render obvious to one skilled in the art the use of an ACE inhibitor for the treatment of inflammatory bowel disease.

Accordingly, Applicants respectfully request that the rejection of Claims 1-5 and 18-23 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance. Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Dated: May 8, 2007

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[4] *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988).